REMARKS

I. 35 U.S.C. 102(b)

Reconsideration is requested of the rejection of claims 1-3, 58, 60, 97, 98, 100, 104, and 105 under 35 U.S.C. 102(b) as being unpatentable over Byas-Smith (U.S. Patent No. 5,762,963).

As amended, claim 1 is directed to a method of treating an organism for a condition mediated by COX-2 expression. The method comprises orally, parenterally, or rectally administering to the organism having such a condition a composition comprising a COX-2 inhibiting amount of an extract of *Capsicum frutescens*.

Byas-Smith discloses methods and compositions for the oral delivery of an increasing amount of capsaicin, capsaicin derivatives, or capsaicin analogs, and one or more capsaicinoids, for the relief of oral and pharyngeal pain while minimizing side effects such as nausea and burning typically associated with the oral administration of capsaicinoids. It is further disclosed that indications that may be treated by the disclosed methods and compositions include all inflammatory pain and neuropathic pain conditions involving the oral cavity, oral pharynx, and other painful mucosal pathology along the course of the gastrointestinal tract.

Significantly, the only disclosure of the use of capsaicin to treat arthritis is a reference in the Background of the Invention to homogenous capsaicin-containing creams for topical application (specifically, Zostrix®, Zostrix-hP®, and Axsain®) that have been shown to be useful in managing the painful conditions (*i.e.* the pain related to) arthritis and osteoarthritis. There is no disclosure to indicate that capsaicin-based compositions can be administered by means other than topically to treat arthritis, or that the same can be used to inhibit COX-2.

Moreover, Byas-Smith does not disclose administration of an extract that inhibits COX-2. Instead, Byas-Smith discloses the administration of a compound that depletes Substance P. Specifically, the disclosed activity of capsaicin is attributable to its ability to deplete local sensory terminals of Substance P, a neurotransmitter for the communication of pain and itch sensations and mediation of inflammation in the skin.[1] There is no indication that the composition of Byas-Smith could inhibit COX-2, or that the depletion of Substance P, a

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[1] Byas-Smith, Column 3, line 55 to Column 4, line 9.

neurotransmitter, and the inhibition of COX-2, an enzyme involved in the production of prostaglandins, are related such that a composition that acts to deplete Substance P would also inhibit COX-2. Therefore, there is no disclosure in Byas-Smith of the ability of a *C. frutescens* extract to inhibit COX-2, or the administration of the same to treat a mammal suffering from a condition mediated by COX-2 expression.

Furthermore, the composition of Byas-Smith, when administered to a mammal, would not inherently inhibit COX-2. Capsaicin is obtained by more than mere methanol extraction of a capsicum fruit. Specifically, Holt et al. and Barr et al., both cited by the Office in the present Office action, state that capsaicin is a white crystalline material obtained from a liquid concentrate, the liquid concentrate being an extract of dry, powdered capsicum fruit.[2] The reference to a white crystalline powder, in addition to the formula of capsaicin disclosed in Byas-Smith, indicate that the capsaicin of Byas-Smith is a purified compound, and is more than a mere methanol extract. Therefore, even assuming that an extract would demonstrate COX-2 inhibiting activity, it cannot be said that any given compound purified therefrom would unavoidably retain such COX-2 inhibiting activity. Therefore, there is no indication in Byas-Smith, nor any reason to believe, that the composition of by Byas-Smith would unavoidably inhibit COX-2.[3] Consequently, the Office's inherency rejection is not properly supported.[4]

Accordingly, Byas-Smith has failed to disclose each and every element of claim 1, and therefore, cannot anticipate claim 1.

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[2] See, Holt et al., U.S. Patent No. 6,348,501, at Column 2, lines 6-10, and Barr et al., U.S. Patent No. 6,197,823, at Column 3, lines 13-17.

[3] Inherency can be found only where attainment of a claimed feature is unavoidable, not where it is merely possible or even probable; *Continental Can v. Monsanto*, 20 USPQ2d 1746 (Fed. Cir. 1991); *ex parte Keith*, 154 USPQ 320 (PTO Bd App 1966); *in re Oelrich*, 212 USPQ 323 (CCPA 1981); *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

[4] To properly support a determination of inherency, as a matter of Patent Office practice, it is incumbent on the Examiner to provide rationale or evidence. See MPEP § 2112.

Claims 2, 3, 58, 60, 97, 98, 100, 104, and 105 depend from claim 1 and are patentable over Byas-Smith for the reasons stated with respect to claim 1 and by reason of the additional requirements which they introduce.

II. 35 U.S.C. 102(e)

Reconsideration is requested of the rejection of claims 1-3, 58, 60, 97, 98, 100, 104, and 105 under 35 U.S.C. 102(e) as being unpatentable over De Lucca, II et al. (U.S. Patent No. 6,310,091).

Claim 1, as amended, is directed to a method of treating an organism for a condition mediated by COX-2 expression.

De Lucca, II et al. disclose an antifungal compound isolated from *C. frutescens*, designated CAY-1. CAY-1 is obtained by the extraction of *C. frutescens* with a suitable solvent, followed by separation of the solid and liquid fraction, elution of the liquid fraction with methanol, and then further purification to homogeneity from the methanol eluate such as by liquid chromatography, high performance liquid chromatography, or the like. CAY-1 is disclosed only to have antifungal properties and can be administered to animals through various routes, including orally, rectally, and parenterally.

Significantly, and similar to Byas-Smith, the only disclosure of the use of capsaicin to treat arthritis in De Lucca, II et al. is a reference in the Background of the Invention to the topical creams Zostrix® and Axsain®. There is no disclosure to indicate that capsaicin-based compositions can be administered by means other than topically to treat arthritis, or that the same can be used to inhibit COX-2.

Moreover, De Lucca, II et al. do not disclose administration of an extract that inhibits COX-2. Instead, De Lucca, II et al. disclose a purified, single compound, CAY-1, obtained from *C. frutescens* and demonstrating antifungal activity. CAY-1 is one of but a few compounds that have been isolated from this particular pepper family.[5] There is no disclosure within De Lucca, II et al. of the ability of CAY-1 to inhibit COX-2, either selectively or otherwise, or that the

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[5] De Lucca, II et al. at Column 3, line 53, and Column 4, line 28.

inhibition of fungal growth and the inhibition of COX-2 are related such that a composition that inhibits fungal growth would also inhibit COX-2. Therefore, there is no disclosure in De Lucca, II et al. of the ability of a *C. frutescens* extract to inhibit COX-2, or the administration of the same to treat a mammal suffering from a condition mediated by COX-2 expression.

Furthermore, there is no indication that the compound disclosed in De Lucca, II et al. is the composition used in the method of claim 1. Specifically, De Lucca, II et al. disclose a compound that is purified to homogeneity[6] and that demonstrates antifungal activity. De Lucca, II et al. disclose that the isolation of CAY-1 required extraction of *C. frutescens*, followed by the additional steps of separation of the liquid and solid phases, elution of the liquid phase, and further purification techniques such as liquid chromatography, high performance liquid chromatography, or the like.[7] Therefore, even assuming that the initial extract of De Lucca, II et al. would demonstrate COX-2 inhibiting activity, it cannot be said that the CAY-1 compound purified therefrom would unavoidably retain such COX-2 inhibiting activity. Therefore, there is no indication in De Lucca, II et al., nor any reason to believe, that the compound of by De Lucca, II et al. would unavoidably inhibit COX-2.[8] Consequently, the Office's inherency rejection is not properly supported.[9]

Accordingly, De Lucca, II et al. have failed to disclose each and every element of claim 1, and therefore, cannot anticipate claim 1.

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[6] De Lucca, II et al., at Column 4, line 28.

[7] De Lucca, II et al., at Column 5, lines 10-31; *See also*, Example 1 at Column 7, line 30 through Column 8, line 2.

[8] Inherency can be found only where attainment of a claimed feature is unavoidable, not where it is merely possible or even probable; *Continental Can v. Monsanto*, 20 USPQ2d 1746 (Fed. Cir. 1991); *ex parte Keith*, 154 USPQ 320 (PTO Bd App 1966); *in re Oelrich*, 212 USPQ 323 (CCPA 1981); *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

[9] To properly support a determination of inherency, as a matter of Patent Office practice, it is incumbent on the Examiner to provide rationale or evidence. See MPEP § 2112.

Claims 2, 3, 58, 60, 97, 98, 100, 104, and 105 depend from claim 1 and are patentable over De Lucca, II et al. for the reasons stated with respect to claim 1 and by reason of the additional requirements which they introduce.

III. 35 U.S.C. 103(a)

A. De Lucca, II et al. or Byas-Smith taken with Hawley's Condensed Chemical Dictionary

Reconsideration is requested of the rejection of claims 1-3, 58, 60, and 97-105 under 35 U.S.C. 103(a) as being unpatentable over De Lucca, II et al. or Byas-Smith taken with Hawley's Condensed Chemical Dictionary ("Hawley's").

Claim 1, as amended, is directed to a method of treating an organism for a condition mediated by COX-2 expression.

De Lucca, II et al. suggest the use of a compound isolated and purified from *C. frutescens*, designated CAY-1, as an antifungal and further disclose the existence of topical creams based upon capsaicin for the treatment of pain related to arthritis. De Lucca, II et al. does not anticipate the presently claimed invention for the reasons stated above in Section II.

Byas-Smith suggests the relief of oral or pharyngeal pain by the administration of an increasing amount of capsaicin, a purified compound, resulting in the depletion of Substance P from local sensory terminals, and, similar to De Lucca, II et al., further discloses the existence of topical creams based upon capsaicin for the treatment of the pain associated with arthritis. Byas-Smith does not anticipate the presently claimed invention for the reasons stated above in Section I.

Hawley's merely demonstrates that methylene chloride (dichloromethane) can be used for solvent extraction. It does not demonstrate the use of the solvent to extract *C. frutescens*.

Even when combined, these three references fail to teach or suggest all limitations of claim 1. There is nothing contained within the references, either singly or in combination, that suggests that an extract of *C. frutescens* has COX-2 inhibiting activity or that compositions containing such an extract could be used to inhibit COX-2. Furthermore, the references do not

teach administering such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2 or administering such a composition in a COX-2 inhibiting amount. Because the combination of references fails to teach or suggest all such claim limitations, the Office has failed to establish a *prima facie* case of obviousness.[10]

Claims 2, 3, 58, 60, and 97-105 depend from claim 1 and are patentable over De Lucca, II et al. or Byas-Smith taken with Hawley's for the reasons stated with respect to claim 1 and by reason of the additional requirements which they introduce.

B. Holt et al., Stevens, Barr et al. or Caruso in view of De Lucca, II et al. or Byas-Smith and Hawley's

Reconsideration is requested of the rejection of claims 1-3, 58, 60, and 97-105 under 35 U.S.C. 103(a) as being unpatentable over Holt et al. (U.S. Patent No. 6,348,501), Stevens (U.S. Patent No. 4,324,785), Barr et al. (U.S. Patent No. 6,197,823), or Caruso (U.S. Patent No. 6,277,398) in view of De Lucca, II et al. or Byas-Smith and Hawley's.

Claim 1 is directed to a method of treating an organism for a condition mediated by COX-2 expression.

Holt et al. disclose a topical lotion for treating the symptoms of arthritis containing capsaicin, an anesthetic, and an analgesic. The lotion is used to treat the pain associated with arthritis. Holt et al. do not anticipate the presently claimed invention, as they do not disclose an extract of *C. frutescens* having COX-2 inhibiting activity, the administration of such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2, or the administration of such a composition in a COX-2 inhibiting amount.

Stevens discloses a powder for use on feet exposed to the cold to provide a feeling of warmth comprising different amounts and combinations of powdered cayenne pepper, powdered ginger, powdered mustard, and at least one powdered aromatic substance. In the Background of the Invention, Stevens discloses that heat producing preparations providing a sense of warmth to painful areas of the body are well known, including preparations comprising capsicum oleoresin,

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[10] MPEP §2142.

for the treatment of muscle pain and arthritis. Stevens does not anticipate the presently claimed invention, as she does not disclose an extract of *C. frutescens* having COX-2 inhibiting activity, the administration of such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2, or the administration of such a composition in a COX-2 inhibiting amount.

Barr et al. disclose topical creams, ointments, foams, and the like, that contain capsaicin and that can be used to treat pain and discomfort associated with disorders such as arthritis. Barr et al. do not anticipate the presently claimed invention, as they do not disclose an extract of *C. frutescens* having COX-2 inhibiting activity, the administration of such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2, or the administration of such a composition in a COX-2 inhibiting amount.

Caruso discloses an analgesic drug composition containing a capsaicinoid, such as capsaicin, as an analgesic component, and dextromethorphan, its active metabolite, dextrorphan, and/or a pharmaceutically acceptable salt thereof, as a potentiator for the capsaicinoid, thereby enhancing its analgesic effect. Caruso discloses that the analgesic drug composition can be formulated for oral, topical, parenteral, etc. administration. Only a topical, nonocclusive drug composition delivery device is demonstrated. The only disclosure of the use of the analgesic drug composition for the treatment of arthritis is the topical application of the composition in combination with a penetration enhancer for the treatment of pain associated with rheumatoid arthritis. Caruso does not anticipate the presently claimed invention, as he does not disclose an extract of *C. frutescens* having COX-2 inhibiting activity, the administration of such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2, or the administration of such a composition in a COX-2 inhibiting amount.

De Lucca, II et al. suggest the use of a compound isolated and purified from *C. frutescens*, designated CAY-1, as an antifungal and further disclose the existence of topical creams based upon capsaicin for the treatment of pain related to arthritis. De Lucca, II et al. does not anticipate the presently claimed invention for the reasons stated above in Section II.

Byas-Smith suggests the relief of oral or pharyngeal pain by the administration of an increasing amount of capsaicin, a purified compound, resulting in the depletion of Substance P from local sensory terminals, and, similar to De Lucca, II et al., further discloses the existence of topical creams based upon capsaicin for the treatment of the pain associated with arthritis. Byas-Smith does not anticipate the presently claimed invention for the reasons stated above in Section I.

Hawley's merely demonstrates that methylene chloride (dichloromethane) can be used for solvent extraction.

Even when combined, these three references fail to teach or suggest all limitations of claim 1. There is nothing contained within the references, either singly or in combination, that suggests that an extract of *C. frutescens* has COX-2 inhibiting activity or that compositions containing such an extract could be used to inhibit COX-2. Furthermore, the references do not teach administering such a composition which inhibits COX-2 activity to an organism having a condition mediated by the expression of COX-2 or administering such a composition in a COX-2 inhibiting amount. Because the combination of references fails to teach or suggest all such claim limitations, the Office has failed to establish a *prima facie* case of obviousness.[11]

Claims 2, 3, 58, 60, and 97-105 depend from claim 1 and are patentable over Holt et al., Stevens, Barr et al., or Caruso in view of De Lucca, II et al. or Byas-Smith and Hawley's for the reasons stated with respect to claim 1 and by reason of the additional requirements which they introduce.

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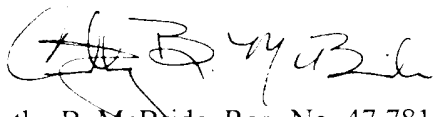
[11] MPEP §2142.

CONCLUSION

In light of the above arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 58, 60, 97, 98, 100, 104, and 105 under 35 U.S.C. 102(b) and 102(e) and of claims 1-3, 58, 60, and 97-105 under 35 U.S.C. 103(a).

Applicants request an extension of time to and including January 24, 2003, for filing a response to the above-mentioned Office action. A check in the amount of the applicable extension fee is enclosed. The Commissioner is hereby authorized to charge any deficiency or overpayment in connection with this amendment to Deposit Account No. 19-1345.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A method of treating [for inhibiting the activity of COX-2 in] an organism for a condition which is mediated by COX-2 expression, the method comprising the step of administering to the organism a composition comprising a therapeutically or prophylatically effective COX-2 inhibiting amount of an organic extract of a plant, wherein the extract selectively inhibits the activity of COX-2 relative to COX-1 as determined in vitro by an IC_{50} ratio of COX-1/COX-2, and wherein the plant is selected from the order consisting of Agavales, Apocynales, Arales, Asterales, Basidiomycetae, Brassicales, Caryophyllales, Cycadales, Ebenales, Euphorbiales, Fagales, Hydrocharitales, Lamiales, Liliales, Loasales, Malvales, Myrtales, Palmales, Pandanales, Papaverales, Piperales, Polemoniales, Polygalales, Primulales, Ranales, Rhamnales, Rosales, Rubiales, Rutales, Santalales, Sapindales, Scrophulariales, Umbellales, Urticales, and Violales.

3. (amended) The method of claim 1 wherein the inhibitory effect of the extract on COX-2 activity is greater than or equal to about 10 times greater than the inhibitory effect of the extract on COX-1 activity.